REMARKS

Claims 53 and 63-87 are pending in this Application. The Applicants have cancelled claims 54-62 without prejudice to their rights to pursue the subject matter of these claims in this or other applications. Applicants have added new claims 63-87 which more clearly define the subject matter of the invention and properly fall within the subject matter of the elected claims. Support for newly added claims 63-87 is found throughout the specification, in particular in canceled claims 54-62, in originally filed claims 14 and 15, and in paragraphs [0120] to [0124] as well as paragraphs [0332] and [0333]. No new matter has been entered.

Objections

The office action states that the amendment filed July 28, 2004, is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure, the new matter being the incorporation by reference of newly added priority document 10/601,518. Accordingly, Applicant has amended the incorporation by reference phrase to remove reference to 10/601,518. In light of this amendment, Applicant respectfully requests reconsideration and withdrawal of the objection to the specification.

112, 2nd paragraph

Claim 55 is rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which the Applicant regards as the invention. More particular the phrase "unfractionated samples of lysed blood" has been objected to.

Claim 55 has been cancelled by the Applicant, see above. However, the Applicant respectfully traverses the rejection as it would apply to any of the newly added and/or amended claims. Applicant notes that the many embodiments of blood samples disclosed in the specification do not render the referenced phrase indefinite. However, for the purposes of expediting prosecution, Applicant has deleted the phrase "unfractionated samples of lysed blood" from the pending claims, and replaced it with the

phrase "unfractionated cells of a lysed blood sample", as noted in newly added claims 68, 69, 70 and 74-76. The phrase "unfractionated cells of a lysed blood sample" is supported, for example, by Example 5, paragraph [0280] of the published application US20060134637 (hereinafter the "Published Application"), which, as noted in the instant office action, includes a centrifugation step after lysis whereby the resulting pellet containing RNA is then further utilized for quantitative PCR.

In view of this amendment and remarks clarifying the claimed embodiments, Applicant respectively contends that this rejection be reconsidered and withdrawn.

112,1st paragraph, written description

Claim 55 is rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

The office action states that the limitation "unfractionated samples of lysed blood" appears to be new matter. Applicant traverses the rejection, but has removed the referenced phrase from the pending claims, solely for the purposes of advancing prosecution.

In view of this amendment and remarks, Applicant respectively requests that this rejection be reconsidered and withdrawn.

112,1st paragraph, enablement

Claims 53-62 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement.

The Applicant respectfully traverses the rejection.

Nature of the Invention and Scope of claims

The office action states:

"the independent claim, as written, states that a comparison of a human test subject IGFPB7 RNA level in a blood sample to a control indicates that bladder cancer is present in the test subject"

"the claims are extremely broad because they require set forth that any or all comparisons between a test subject and a control subject is indicative of disease."

and "control subjects would could encompass patients with bladder cancer, healthy patients, patients with some other disease, such as obesity or heart failure, patients with a particular stage of bladder cancer, etc."

see p. 5 of the office action dated March 26, 2007 (hereinafter the "Office Action")

The Applicant respectfully disagrees that any comparison is sufficient to indicate the presence of bladder cancer in the test subject particularly in light of the newly amended claims. The Applicant has amended claim 53 (and corresponding independent claims 65 and 68) so as to require that the comparison of the level of IGFPB7 RNA in the blood sample of the test subject as compared with the level in blood of control subjects having bladder cancer results in a "statistically significant similarity" to be indicative of bladder cancer in the test subject. Newly added claim 63 (and corresponding independent claims 66 and 69) require that there be a comparison of the level of IGFPB7 RNA in the test subject with the level in **both (i)** control subjects not having bladder cancer **and** (ii) control subjects having bladder cancer. Furthermore, the comparison must result in (i) a "statistically significant similarity" between the level of RNA in the blood sample of the test subject as compared with the level of RNA in blood of the control subjects having bladder cancer **and** (ii) a "statistically significant difference" between the level of RNA in the blood sample of the test subject as compared with the level of RNA in blood of the control subjects not having the bladder cancer in order to be indicative of the bladder cancer in the test subject. Newly added claim 64 (and corresponding independent claims 67 and 70) similarly require that there be **both** a "statistically significant difference" between the level of RNA in the blood sample of the test subject as compared with the level of RNA in blood of healthy control subjects **and** a "statistically significant similarity" between the level of RNA in the blood sample of the test subject as compared with the level of RNA in blood of control subjects who have bladder cancer.

Thus the "control subjects" do not encompass patients with bladder cancer, healthy patients, patients with some other disease, such as obesity or heart failure, and patients with a particular stage of bladder cancer as suggested at p.5 of the Office Action. Rather the control subjects either have the bladder cancer of interest (ie the specific stage of bladder cancer that is being tested for), they do not have the bladder cancer of interest or they are healthy control subjects. Furthermore, the comparison alone, no matter the result of the comparison, is not sufficient to indicate bladder cancer as suggested at p. 6 of the Office Action. Instead, the comparison of the levels of the test subject with at least one set of the defined control subjects must result in a significant similarity, and in some cases, the test subject is being compared both with a negative and a positive control and a determination of a significant similarity with the positive control and a significant difference with the negative control results in the determination that is indicative of disease in said test subject. Furthermore, the similarity or difference must be one with a statistical degree of significance, as determined by the many statistical techniques widely used in assessing the use of specific biomarkers in diagnosis, including those statistical techniques referenced in the instant specification, and incorporated by reference.

Therefore the methods as outlined in the independent claims do not permit "any level and direction of difference in gene expression to be indicative of disease" as suggested at p.6 of the Office Action.

Differential Expression and Predictability

The office action states that the claims do not "set forth the direction of the difference necessary to indicate bladder disease" (p. 6 of the Office Action) and suggests that without providing this information, the mere observation of differences is an unpredictable indicator of bladder cancer.

The Applicant respectfully submits that the invention is taught in such terms that one skilled in the art can make and use the claimed invention, including the use of the elected biomarker IGFBP7 as an indicator of bladder cancer as described in the claims without disclosing the direction or the level of difference that exists between patients having bladder cancer and individuals not having bladder cancer. The Applicant has

identified the elected gene IGFBP7 as differentially expressed as between individuals diagnosed as having bladder cancer and individuals not having bladder cancer by demonstrating a statistical difference in the level of RNA, as described in Example 19. The statistical significance of IGFBP7's differential expression is evidenced by its P value of 3.26E-04 as listed in Table 3J, acknowledged by the office action. The identification of IGFPB7 in Figure 17 demonstrates that the gene is one of a number of genes which demonstrate a statistically significant difference as between a population of 5 individuals who have bladder cancer and 18 individuals not having bladder cancer (as noted by the dendrogram). Therefore the Applicant has taught that there is a significant difference in differential expression for IGFBP7 as between a population of individuals having bladder cancer and a population of individuals not having bladder cancer, and further has taught to compare the level of expression of IGFBP7 in a test individual with populations having bladder cancer and populations not having bladder cancer using classification methods to determine the similarity or difference in gene expression levels as between the test subject and the tested populations (see paragraphs [0117] to [0119] and [0123] to [0126] in addition to [0333]. All of the claims require that the level of expression of RNA corresponding to IGFBP7 be compared with the level of IGFBP7 in other individuals who have bladder cancer and require at minimum a statistically significant similarity as between the test subject and control subjects having bladder cancer before the level of gene expression of IGFBP7 is considered to be indicative of bladder cancer.

Furthermore, the Applicant contends that it does not require undue experimentation for one of skill to determine the inherent direction or level of the statistically significant differential expression required for the claimed methods of detecting a bladder cancer, given the widely established and validated analytical tools for analyzing gene expression levels. Therefore, it is not necessary for the Applicant to have taught the exact direction or level of difference between the two populations. The Applicant has provided sufficient information by teaching that there is a difference and that it is significant as between the populations.

The Office Action also suggests that "observing differences in expression between two populations is highly unpredictable" (p.7 of the Office Action). The Applicant submits that the differential expression of IGFBP7 as between patients having bladder cancer and patients not having bladder cancer is, in fact, predictable. The predictability is evidenced by the post filing research article, Osman et al., cited in the office action (hereinafter "Osman et al."). In Osman et al., blood cell gene expression profiles of an even greater number of bladder cancer patients (ie.16 individuals having bladder cancer) were compared with 10 healthy individuals. A selection of the genes identified as demonstrating statistically significant difference ($P<0.05$) (p.3376) were tested using RT-PCR on yet an additional sample set of 20 bladder cancer patients and 14 control patients (p. 3376, second column) and IGFBP7 continued to verify as a gene which was differentially expressed as between the two populations (see page 3377, second column). As stated in the Manual of Patent Examining Procedure at 2164.03: the "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. In this case the disclosed result is a statistically significant difference in the level of IGFBP7 RNA as between individuals having bladder cancer and individuals not having bladder cancer. This statistically significant difference is confirmed by post filing references. The claimed invention requires a statistically significant similarity between the level of expression of IGFPB7 between the test subject and individuals having bladder cancer so as to be indicative of bladder cancer in the test subject. One skilled in the art can readily anticipate that there is similarity as between the level of expression in the test subject and a level of expression in patients having bladder cancer – knowing that the level is significantly different between subjects having bladder cancer and subjects not having bladder cancer, then there is predictability in the art.

The fact that Applicant discloses that the IGFBP7 gene is also differentially expressed in obesity is not detrimental to either the value or enablement of the use of IGFBP7 gene as a biomarker which is indicative of bladder cancer. The Applicant has, in fact, demonstrated that IGFBP7 is not identified as differentially expressed in a statistically significant manner in any other of the many diseases tested. The specificity of IGFBP7 is further confirmed by Osman et al. which notes that IGFBP7 is also

differentially expressed when comparing bladder cancer patients with patients diagnosed as having either testicular cancer or kidney cancer (see p. 3377, second column, last paragraph). Irrespective of this fact, the requirement within the claims of a statistically significant similarity as between the test subject and control subjects having bladder cancer helps ensure that the level of expression being detected is selectively indicative of bladder cancer and not any other disease condition since it would be highly unlikely that the level and/or direction of expression in patients with bladder cancer would be statistically similar to the level of expression in patients with other non-related diseases.

Furthermore, the use of a biomarker as an indication of disease, is typically just one aspect of a multi-factorial process used for diagnosing the patient. For example, as noted in Stedman's 27th Edition Medical Dictionary, "indication" is not equated with "diagnosis". The term *"indication"* is understood to mean "**the basis for initiation** of a treatment for a disease or **of a diagnostic test"** (p. 892). Even a *"diagnostic test"* is not considered to result in an absolute certainty of a diagnosis – but rather is noted as "**relating to or aiding in diagnosis**". As noted in Harrison's Principles of Internal Medicine, Introduction to Clinical Medicine "the purpose of performing a test on a patient is to reduce uncertainty about the patient's diagnosis or prognosis and to aid the clinician in making management decisions" (Ch I, pg. 11). This same text further notes that while "a perfect test would have a sensitivity of 100% and a specificity of 100% and would completely separate patients with disease from those without it...there are no perfect tests, after every test is completed the true disease state of the patient remains uncertain" (Ch I, pg. 11). Therefore, the possibility that a person with obesity might be mischaracterized as having bladder cancer, which as noted above is highly unlikely, does not detract from the utility of the biomarkers as an indication of bladder cancer. Rather such a hypothetical result would merely reduce the specificity of the biomarker in a limited subpopulation of individuals.

The office action also suggests that the Applicant has not taught that the elected gene alone is sufficient to detect bladder cancer (see p. 9 of the Office Action). The Applicant notes that it is not aware of any teaching or suggestion of looking in blood for biomarkers indicative of bladder cancer prior to applicant's filing, and it is only as a

result of the USPTO's policy regarding restriction requirements that the Applicant has been forced to narrow the claims to a specific gene or set of genes. Furthermore, the Applicant has demonstrated, both within the specification, and in post filing art that the differential expression of the elected gene is statistically significant as between individuals having bladder cancer and individuals not having bladder cancer – itself demonstrating that the elected gene is indicative of bladder cancer. The fact that post-filing reference Osman et al. demonstrates that the elected gene can be used in combination with other genes for a diagnostic test which is highly sensitive and highly specific, (see pg. 3377 and Figure 2 of Osman et al.) is merely confirmation that the elected gene is indicative of bladder cancer.

The final concern raised in the office action with respect to enablement is the inherent limitations of biomarker technology raised in the Osman et al paper, specifically the putative limitation that the profiles may be limited to a cohort of patients. The Applicant would note that in the Office Action dated August 28, 2006 for U.S. patent application number 10/268,730 (the parent application of the continuation-in-part from which this divisional is derived), pre-filing reference Nagai et al. (Neurology 46 March 1996) is considered to teach a change in expression which is indicative of the disease Parkinson's (see p. 17 of the Office Action dated August 28, 2006 for 10/268,730) because work was carried out to identify the marker gene and establish a statistically significant relationship between the disease phenotype and the differential expression (see p. 9 of the Office Action dated August 28, 2006 for 10/268,730). The Applicant notes that Nagai et al. established D3R as a biomarker indicative of Parkinson's utilizing 22 patients with PD and 18 control patients (see p.793 of Nagai et al., column 1) which is approximately one-half the number of patients tested in Osman et al., which utilized at least 40 bladder cancer patients and 27 controls (see p. 3376 last sentence, and p. 3377 first sentence). Therefore, Applicants contend that Osman et al.'s discussion regarding the outside possibility that the cohort of bladder cancer patients tested may not be representative of bladder cancer patients in general, does not diminish the enablement of the claimed methods.

In light of the amendments and above remarks, the Applicant contends that the claims are fully enabled, and respectfully request reconsideration and withdrawal of the instant rejection.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted, Amy DeClaus

Date: June 26, 2007

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Excerpts from Stedman, Thomas Lathrop, 1853-1938, Stedman's Medical Dictionary 27th Edition, ed. Lippincott Williams & Wilkins, p. 492, 892,
Excerpts from Harrison's Principles of Internal Medicine, ch I Introduction to Clinical Medicine, p. 11.

STEDMAN'S Medical Dictionary

27th Edition

Illustrated in Color

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therapeutic i., the ratio of LD_{50} to ED_{50}, used in quantitative comparison of drugs.

thoracic i., anteroposterior diameter of the thorax times 100 divided by the transverse diameter of the thorax. SYN chest i.

tibiofemoral i., the ratio obtained by multiplying the length of the tibia by 100 and dividing by the length of the femur.

transversovertical i., SYN vertical i.

tuberculoopsonic i., the opsonic i. calculated in relation to tuberculous infection, with an actively growing culture of *Mycobacterium tuberculosis* or the strain of tubercle bacillus from the patient being used in the test.

ultraviolet i., a daily i. issued by the U.S. National Weather Service for many cities, forecasting the amount of dangerous ultraviolet light that will arrive at the earth's surface about noon the following day.

uricolytic i., the percentage of uric acid oxidized to allantoin before being secreted.

vertical i., the relation of the height to the length of the skull: (height × 100)/length. SYN height-length i., length-height i., transversovertical i.

vital i., the ratio of births to deaths within a population during a given time.

Volpe-Manhold i. (V-MI), an index for comparing the amount of dental calculus in individuals.

volume i., an indication of the relative size (e.g., volume) of erythrocytes, calculated as follows: hematocrit value, expressed as per cent of normal ÷ red blood cell count, expressed as per cent of normal = volume i.

zygomaticoauricular i., the ratio between the zygomatic and the auricular diameters of the skull or head.

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in·di·can (in'di-kan). **1.** Indoxyl β-D-glucoside from *Indigofera* species and *Polygonium tinctorium;* a source of indigo. SYN plant i. **2.** 3-Indoxylsulfuric acid, a substance found (as its salts) in sweat and in variable amounts in urine; indicative, when in quantity, of protein putrefaction in the intestine (indicanuria). SYN metabolic i., uroxanthin.

metabolic i., SYN indican (2).

plant i., SYN indican (1).

in·di·can·i·dro·sis (in'di-kan-i-drō'sis). Excretion of indican in the sweat. [indican + G. *hidrōs*, sweat]

in·di·cant (in'di-kant). **1.** Pointing out; indicating. **2.** An indication; especially a symptom indicating the proper line of treatment. [L. *in-dico*, pres. p. *-ans* (*-ant*), to point out]

in·di·can·u·ria (in'di-kan-ū'rē-ă). An increased urinary excretion of indican, a derivative of indol formed chiefly in the intestine when protein is putrefied; indol is also formed during the putrefaction of protein in other sites.

in·di·ca·tion (in-di-kā'shŭn). The basis for initiation of a treatment for a disease or of a diagnostic test; may be furnished by a knowledge of the cause (**causal i.**), by the symptoms present (**symptomatic i.**), or by the nature of the disease (**specific i.**). [L. fr. *in-dico*, pp. *-atus*, to point out, fr. *dico*, to proclaim]

off label i., use of a medication for a purpose other than that approved by the FDA.

in·di·ca·tor (in'di-kā-ter, -tōr). **1.** In chemical analysis, a substance that changes color within a certain definite range of pH or oxidation potential, or in any way renders visible the completion of a chemical reaction; e.g., litmus, phenolsulfonphthalein. **2.** An isotope that is used as a tracer. **3.** The labeled substance whose distribution between reactants of a system is used to determine the amount of analyte present. [L. one that points out]

alizarin i., a solution consisting of 1 g sodium alizarin sulfonate dissolved in 100 mL distilled water; used as an i. for free acidity in gastric contents.

clinical i., a measure, process, or outcome used to judge a particular clinical situation and indicate whether the care delivered was appropriate.

health i., variable, susceptible to direct measurement, that reflects the state of health of persons in a community.

oxidation-reduction i., a substance that undergoes a definite color change at a specific oxidation potential. SYN redox i.

redox i., SYN oxidation-reduction i.

in·di·ces (in'di-sēz). Alternative plural of index.

In·di·el·la (in-dē-el'ă). Old name for *Madurella*.

in·dig·e·nous (in-dij'ĕ-nŭs). Native; natural to the country or region where found. [L. *indigenus*, born in fr. *indu*, within (old form of *in*), + G. *-gen*, producing]

in·di·ges·tion (in-di-jes'chŭn). Nonspecific term for a variety of symptoms resulting from a failure of proper digestion and absorption of food in the alimentary tract.

acid i., i. resulting from hyperchlorhydria; often used by the laity as a synonym for pyrosis.

fat i., SYN steatorrhea.

gastric i., SYN dyspepsia.

nervous i., i. caused by emotional upsets or stress.

in·di·go (in'dī-gō) [C.I. 73000]. A blue dyestuff obtained from *Indigofera tinctoria*, and other species of *Indigofera* (family Leguminosae); also made synthetically. SYN indigo blue, indigotin. [L. *indicum*, fr. G. *indikon*, indigo, ntr. of *Indikos*, Indian]

in·di·go blue. SYN indigo.

in·di·go car·mine [C.I. 73015]. A blue dye used for measurement of kidney function and as a special stain for Negri bodies. SYN sodium indigotin disulfonate.

in·dig·o·tin (in-dig'ō-tin, in-di-gō'tin). SYN indigo.

in·di·go·u·ria, in·di·gu·ria (in'dī-gō-ū'rē-ă, in-di-goo'rē-ă). The excretion of indigo in the urine.

in·dis·po·si·tion (in-dis-pō-zish'ŭn). Illness, usually slight; malaise. [L. *in* neg. + *dispositio*, an arrangement, fr. *dis-pono*, pp. *-positus*, to place apart]

in·di·um (In) (in'dē-ŭm). A metallic element, atomic no. 49, atomic wt. 114.82. [*indigo*, because of its blue line in the spectrum]

in·di·um-111 (^{111}In). A cyclotron-produced radionuclide with a half-life of 2.8049 days and with gamma ray emissions of 171.2 and 245.3 kiloelectron volts. In a chloride form, it is used as a bone marrow and tumor-localizing tracer; in a chelate form, as a cerebrospinal fluid tracer. It is also used as a white blood cell labeling agent and as an antibody label.

i. chloride, i. trichloride, $InCl_3$; used in electron microscopy to stain nucleic acids in thin tissue sections.

in·di·um-113m (^{113m}In). A radioactive isomer of ^{113}In; it has a half-life of 1.658 hours; it has been used in cisternography and as a diagnostic aid in cardiac output.

in·di·vid·u·a·tion (in'di-vid-ū-ā'shŭn). **1.** Development of the individual from the specific. **2.** In jungian psychology, the process by which one's personality is differentiated, developed, and expressed. **3.** Regional activity in an embryo as a response to an organizer.

in·do·cy·a·nine green (in-dō-sī'ă-nēn). A tricarbocyanine dye that binds to serum albumin and is used in blood volume determinations and in liver function tests.

in·do·cy·bin (in-dō-sī'bin). SYN psilocybin.

in·dol·ac·e·tu·ria (in'dōl-as-ĕ-too'rē-ă). Excretion of an appreciable amount of indoleacetic acid in the urine; a manifestation of Hartnup disease, also seen in patients with carcinoid tumors.

in·dol·a·mine (in-dol'ă-mēn). General term for an indole or indole derivative containing a primary, secondary, or tertiary amine group (e.g., serotonin).

in·dole (in'dōl). **1.** 2,3-Benzopyrrole; basis of many biologically active substances (e.g., serotonin, tryptophan); formed in degradation of tryptophan. SYN ketole. **2.** Any of many alkaloids containing the i. (1) structure.

in·do·lent (in'dō-lent). Inactive; sluggish; painless or nearly so, said of a morbid process. [L. *in-* neg. + *doleo*, pr. p. *dolens* (*-ent-*), to feel pain]

in·dol·ic ac·ids (in-dōl'ik). Metabolites of L-tryptophan formed within the body or by intestinal microorganisms; the principal i. a. encountered in urine are indoleacetic acid, indoleacetylglutamine, 5-hydroxyindoleacetic acid, and indolelactic acid.

antenatal d., SYN prenatal d.

clinical d., a d. made from a study of the signs and symptoms of a disease.

differential d., the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings. SYN differentiation (2).

d. by exclusion, a d. made by excluding those diseases to which only some of the patient's symptoms might belong, leaving one disease as the most likely d., although no definitive tests or findings establish that d.

laboratory d., a d. made by a chemical, microscopic, microbiologic, immunologic, or pathologic study of secretions, discharges, blood, or tissue.

neonatal d., systematic evaluation of the newborn for evidence of disease or malformations, and the conclusion reached.

pathologic d., a d., sometimes postmortem, made from an anatomic and/or histologic study of the lesions present.

physical d., (1) a d. made by means of physical examination of the patient. (2) the process of a physical examination.

prenatal d., d. utilizing procedures available for the recognition of diseases and malformations *in utero*, and the conclusion reached. SYN antenatal d.

di·ag·nos·tic (dī-ag-nos'tik). 1. Relating to or aiding in diagnosis. 2. Establishing or confirming a diagnosis.

di·ag·nos·ti·cian (dī'ag-nos-tish'ăn). One who is skilled in making diagnoses; formerly, a name for specialists in internal medicine.

***Diagnostic and Statistical Manual of Mental Disorders* (DSM).** A system of classification, published by the American Psychiatric Association, that divides recognized mental disorders into clearly defined categories based on sets of objective criteria. Representing a majority view (rather than a consensus) of hundreds of contributors and consultants, DSM is widely recognized as a diagnostic standard and widely used for reporting, coding, and statistical purposes.

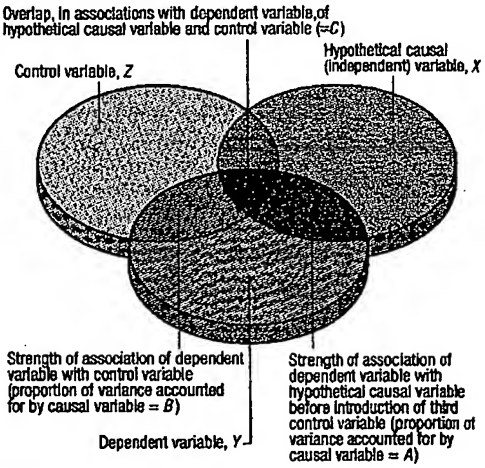
The first edition (1952), based on the sixth revision of the *International Classification of Diseases* (*ICD-6*), was intended to promote uniformity in the naming and reporting of psychiatric disorders. It contained definitions of all named disorders, but no sets of diagnostic criteria. While its classification of mental disorders showed the influence of Freudian psychoanalysis, its nomenclature (e.g., depressive reaction, anxiety reaction, schizophrenic reaction) reflected the theories of Adolf Meyer (1866–1950). The second edition (*DSM-II*, 1968) preserved the psychoanalytic orientation but dropped the "reaction" terminology. The third edition (*DSM-III*, 1980) abandoned much of the rigidly psychodynamic thinking of the earlier editions and, for the first time, provided explicit diagnostic criteria and introduced a multiaxial system whereby different aspects of a patient's condition could be separately assessed. Briefly stated, the axes are I, clinical disorders; II, personality disorders and mental retardation; III, general medical disorders; IV, psychosocial and environmental stressors; and V, overall level of functioning. A revised version of the third edition (*DSM-IIIR*, 1987) incorporated a number of improvements and clarifications. The fourth edition (*DSM-IV*) appeared in May, 1994. It follows its two predecessors closely in general outline, and like them is coordinated with and partly derived from *ICD-9*. For many observers, the most significant change in *DSM-IV* is the renaming of the category formerly called "Organic Mental Syndromes and Disorders" as "Delirium, Dementia, and Amnestic and Other Cognitive Disorders," a shift in terminology intended to avoid the implication that mental disorders in other categories are not organic.

di·a·gram. A simple, graphic depiction of an idea or object.

Dienaide d., SYN triaxial reference *system*.

flow d., a d. composed of blocks connected by arrows representing steps in a process such as decision analysis.

Venn d., pictorial representation of the extent to which two or more quantities or concepts are mutually inclusive and exclusive.



Venn diagram

di·a·ki·ne·sis (dī'ă-ki-nē'sis). Final stage of prophase in meiosis I, in which the chiasmata present during the diplotene stage disappear, the chromosomes continue to shorten, and the nucleolus and nuclear membrane disappear. [G. *dia*, through, + *kinēsis*, movement]

dial (dī'ăl, dīl). A clock face or instrument resembling a clock face. [L. *dies*, day]

astigmatic d., a diagram of radiating lines, used to test for astigmatism.

Di·a·lis·ter (dī-ăl-is'ter). An obsolete name for a genus of bacteria, the type species of which, *D. pneumosintes*, is now placed in the genus *Bacteroides*.

di·al·lyl (dī-al'il). A compound containing two allyl groups.

di·al·y·sance (dī-al'i-sans). The number of milliliters of blood completely cleared of any substance by an artificial kidney or by peritoneal dialysis in a unit of time; conventional clearance formulas are expressed as mm/min. [fr. dialysis]

di·al·y·sate (dī-al'i-sāt). That part of a mixture that passes through a dialyzing membrane; the material that does not pass through is referred to as the retentate. SYN diffusate.

di·al·y·sis (dī-al'i-sis). 1. A form of filtration to separate crystalloid from colloid substances (or smaller molecules from larger ones) in a solution by interposing a semipermeable membrane between the solution and dialyzing fluid; the crystalloid (smaller) substances pass through the membrane into the dialyzing fluid on the other side, the colloids do not. 2. The separation of substances across a semipermeable membrane on the basis of particle size and/or concentration gradients. 3. A method of artificial kidney function. [G. a separation, fr. *dialyo*, to separate]

continuous ambulatory peritoneal d. (CAPD), method of peritoneal d. performed in ambulatory patients with influx and efflux of dialysate during normal activities.

equilibrium d., in immunology, a method for determination of association constants for hapten-antibody reactions in a system in which the hapten (dialyzable) and antibody (nondialyzable) solutions are separated by semipermeable membranes. Since at equilibrium the quantity of free hapten will be the same in the two compartments, quantitative determinations can be made of hapten-bound antibody, free antibody, and free hapten.

extracorporeal d., hemodialysis performed through an apparatus outside the body.

peritoneal d., removal from the body of soluble substances and

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reduces the likelihood of hyperthyroidism in a patient with paroxysmal atrial fibrillation.

While the representativeness and availability heuristics may play the major roles in shaping early diagnostic hypotheses, the acuity of a patient's illness can also be very influential. For example, clinicians are taught to consider aortic dissection routinely as a possible cause of acute severe chest discomfort along with myocardial infarction, even though the typical history of dissection is different from myocardial infarction and dissection is far less prevalent (Chap. 247). This recommendation is based on the recognition that a relatively rare but catastrophic diagnosis like aortic dissection is very difficult to make unless it is explicitly considered. If the clinician fails to elicit any of the characteristic features of dissection by history and finds equivalent blood pressures in both arms and no pulse deficits, he or she may feel comfortable in discarding the aortic dissection hypothesis. If, however, the chest x-ray shows a widened mediastinum, the hypothesis may be reinstated and a diagnostic test ordered [e.g., thoracic computed tomography (CT) scan, transesophageal echocardiogram] to evaluate it more fully. In noncritical situations, the prevalence of potential alternative diagnoses should play a much more prominent role in diagnostic hypothesis generation. The value of conducting a rapid systematic clinical survey of symptoms and organ systems to avoid missing important but inapparent clues cannot be overstated.

Because the generation and evaluation of appropriate diagnostic hypotheses is a skill that not all clinicians possess to an equal degree, errors in this process can occur, and in the patient with serious acute illness these may lead to tragic consequences. Consider the following hypothetical example. A 45-year-old male patient with a 3-week history of a "flulike" upper respiratory infection (URI) presented to his physician with symptoms of dyspnea and a productive cough. Based on the presenting complaint, the clinician pulled out a "URI Assessment Form" to improve quality and efficiency of care. The physician quickly completed the examination components outlined on this structured form, noting in particular the absence of fever and a clear chest examination. He then prescribed an antibiotic for presumed bronchitis, showed the patient how to breathe into a paper bag to relieve his "hyperventilation," and sent him home with the reassurance that his illness was not serious. After a sleepless night with significant dyspnea unrelieved by rebreathing into a bag, the patient developed nausea and vomiting and collapsed. He was brought into the Emergency Department in cardiac arrest and could not be resuscitated. Autopsy showed a posterior wall myocardial infarction and a fresh thrombus in an atherosclerotic right coronary artery. What went wrong? The clinician decided, even before starting the history, that the patient's complaints were not serious. He therefore felt confident that he could perform an abbreviated and focused examination using the URI assessment protocol rather than considering the full range of possibilities and performing appropriate tests to confirm or refute his initial hypotheses. In particular, by concentrating on the "URI," the clinician failed to elicit the full dyspnea history, which would have suggested a far more serious disorder, and did not even search for other symptoms that could have directed him to the correct diagnosis.

This example illustrates how patients can diverge from textbook symptoms and the potential consequences of being unable to adapt the diagnostic process to real-world challenges. The expert, while recognizing that common things occur commonly, approaches each evaluation on high alert for clues that the initial diagnosis may be wrong. Patients often provide information that "does not fit" with any of the leading diagnostic hypotheses being considered. Distinguishing real clues from false trails can only be achieved by practice and experience. A less experienced clinician who tries to be too efficient (as in the above example) can make serious judgment errors.

MAJOR INFLUENCES ON CLINICAL DECISION-MAKING More than a decade of research on variations in clinician practice patterns has shed much light on forces that shape clinical decisions. The use of heuristic "shortcuts," as detailed above, provides a partial explanation, but several other key factors play an important role in shaping diagnostic hypotheses and management decisions. These factors can be grouped conceptually into three overlapping categories: (1) factors related to physician personal characteristics and practice style, (2) factors related to the practice setting, and (3) economic incentive factors.

Practice Style Factors One of the key roles of the physician in medical care is to serve as the patient's agent to ensure that necessary care is provided at a high level of quality. Factors that influence this role include the physician's knowledge, training, and experience. It is obvious that physicians cannot practice evidence-based medicine if they are unfamiliar with the evidence. As would be expected, specialists generally know the evidence in their field better than do generalists. Surgeons may be more enthusiastic about recommending surgery than medical doctors because their belief in the beneficial effects of surgery is stronger. For the same reason, invasive cardiologists are much more likely to refer chest pain patients for diagnostic catheterization than are noninvasive cardiologists or generalists. The physician beliefs that drive these different practice styles are based on personal experience, recollection, and interpretation of the available medical evidence. For example, heart failure specialists are much more likely than generalists to achieve target angiotensin-converting enzyme (ACE) inhibitor therapy in their heart failure patients because they are more familiar with what the targets are (as defined by large clinical trials), have more familiarity with the specific drugs (including dosages and side effects), and are less likely to overreact to foreseeable problems in therapy such as a rise in creatinine levels or symptomatic hypotension. Other intriguing research has shown a wide distribution of acceptance times of antibiotic therapy for peptic ulcer disease following widespread dissemination of the "evidence" in the medical literature. Some gastroenterologists accepted this new therapy before the evidence was clear (reflecting, perhaps, an aggressive practice style), and some gastroenterologists lagged behind (a conservative practice style, associated in this case with older physicians). As a group, internists lagged several years behind gastroenterologists.

The opinion of influential leaders can also have an important effect on practice patterns. Such influence can occur at both the national level (e.g., expert physicians teaching at national meetings) and the local level (e.g., local educational programs, "curbside consultants"). Opinion leaders do not have to be physicians. When conducting rounds with clinical pharmacists, physicians are less likely to make medication errors and more likely to use target levels of evidence-based therapies.

The patient's welfare is not the only concern that drives clinical decisions. The physician's perception about the risk of a malpractice suit resulting from either an erroneous decision or a bad outcome creates a style of practice referred to as *defensive medicine*. This practice involves using tests and therapies with very small marginal returns to preclude future criticism in the event of an adverse outcome. For example, a 40-year-old woman who presents with a long-standing history of intermittent headache and a new severe headache along with a normal neurologic examination has a very low likelihood of structural intracranial pathology. Performance of a head CT or magnetic resonance imaging (MRI) scan in this situation would constitute defensive medicine. On the other hand, the results of the test could provide reassurance to an anxious patient.

Practice Setting Factors Factors in this category relate to the physical resources available to the physician's practice and the practice environment. *Physician-induced demand* is a term that refers to the repeated observation that physicians have a remarkable ability to accommodate to and employ the medical facilities available to them. A classic early study in this area showed that physicians in Boston had an almost 50% higher hospital admission rate than did physicians in New Haven, despite there being no obvious differences in the health of the cities' inhabitants. The physicians in New Haven were not aware of using fewer hospital beds for their patients, nor were the Boston physicians aware of using less stringent criteria to admit patients.

Other environmental factors that can influence decision-making include the local availability of specialists for consultations and procedures, "high tech" facilities such as angiography suites, a heart surgery program, and MRI machines.

Economic Incentives Economic incentives are closely related to the other two categories of practice-modifying factors. Financial issues can exert both stimulatory and inhibitory influences on clinical practice. In general, physicians are paid on a fee-for-service, capitation, or salary basis (Chap. 4). In fee-for-service, the more the physician does, the more the physician gets paid. The incentive in this case is to do more. When fees are reduced (discounted fee-for-service), doctors tend to increase the number of services billed for. Capitation, in contrast, provides a fixed payment per patient per year, encouraging physicians to take on more patients but to provide each patient with fewer services. Expensive services are more likely to be affected by this type of incentive than inexpensive preventive services. Salary compensation plans pay physicians the same regardless of the amount of clinical work performed. The incentive here is to see fewer patients. Recognizing these powerful shapers of physician behavior, managed care plans have begun to explore combinations of the three reimbursement types with the goal of improving individual physician productivity while restraining their use of expensive tests and therapies.

In summary, expert clinical decision-making can be appreciated as a complex interplay between cognitive devices used to simplify large amounts of complex information interacting with physician biases reflecting education, training, and experience, all of which are shaped by powerful, sometimes perverse, external forces. In the next section, we will review a set of statistical tools and concepts that can assist in making clinical decisions under uncertainty.

QUANTITATIVE METHODS TO AID CLINICAL DECISION-MAKING

The process of medical decision-making can be divided into two parts: (1) defining the available courses of action and estimating the likely outcomes with each, and (2) assessing the desirability of the outcomes. The former task involves integrating key information about the patient along with relevant evidence from the medical literature to create the structure of a decision problem. The remainder of this chapter will present some quantitative tools to assist the clinician in these activities. These tools can be divided into those that assist the clinician in making better outcome predictions, which are then used to make decisions, and those that support the decision process directly. While these tools are not yet used routinely in daily clinical practice, the computerization of medicine is creating the required substrate for their future widespread dissemination.

QUANTITATIVE MEDICAL PREDICTIONS **Diagnostic Testing** The purpose of performing a test on a patient is to reduce uncertainty about the patient's diagnosis or prognosis and to aid the clinician in making management decisions. Although diagnostic tests are commonly thought of as laboratory tests (e.g., measurement of serum amylase level) or procedures (e.g., colonoscopy or bronchoscopy), any technology that changes our understanding of the patient's problem qualifies as a diagnostic test. Thus, even the history and physical examination can be considered a form of diagnostic test. In clinical medicine, it is common to reduce the results of a test to a dichotomous outcome, such as positive or negative, normal or abnormal. In many cases, this simplification results in the waste of useful information. However, such simplification makes it easier to demonstrate some of the quantitative ways in which test data can be used.

To characterize the accuracy of diagnostic tests, four terms are routinely used (Table 3-1). The *true-positive rate*, i.e., the sensitivity, provides a measure of how well the test correctly identifies patients with disease. The *false-negative rate* is calculated as (1 − sensitivity). The *true-negative rate*, i.e., the specificity, reflects how well the test correctly identifies patients without disease. The *false-positive rate* is (1 − specificity). A perfect test would have a sensitivity of 100% and a specificity of 100% and would completely separate patients with disease from those without it.

Table 3-1 Measures of Diagnostic Test Accuracy

	Disease Status	
Test Result	Present	Absent
Positive	True-positive (*TP*)	False-positive (*FP*)
Negative	False-negative (*FN*)	True-negative (*TN*)

IDENTIFICATION OF PATIENTS WITH DISEASE

True-positive rate (sensitivity) = $TP/(TP + FN)$
False-negative rate = $FN/(TP + FN)$
True-positive rate = 1 − false-negative rate

IDENTIFICATION OF PATIENTS WITHOUT DISEASE

True-negative rate (specificity) = $TN/(TN + FP)$
False-positive rate = $FP/(TN + FP)$
True-negative rate = 1 − false-positive rate

Calculating sensitivity and specificity require selection of a cut-point value for the test to separate "normal" from "diseased" subjects. As the cutpoint is moved to improve sensitivity, specificity typically falls and vice versa. This dynamic tradeoff between more accurate identification of subjects with versus those without disease is often displayed graphically as a receiver operating characteristic (ROC) curve. An ROC curve plots sensitivity (*y*-axis) versus 1 − specificity (*x*-axis). Each point on the curve represents a potential cutpoint with an associated sensitivity and specificity value. The area under the ROC curve is often used as a quantitative measure of the information content of a test. Values range from 0.5 (no diagnostic information at all, test is equivalent to flipping a coin) to 1.0 (perfect test).

In the diagnostic testing literature, ROC areas are often used to compare alternative tests. The test with the highest area (i.e., closest to 1.0) is presumed to be the most accurate. However, ROC curves are not a panacea for evaluation of diagnostic test utility. Like Bayes' theorem, they are typically focused on only one possible test parameter (e.g., ST segment response in a treadmill exercise test) to the exclusion of other potentially relevant data. In addition, ROC area comparisons do not simulate the way test information is actually used in clinical practice. Finally, biases in the underlying population used to generate the ROC curves (e.g., related to an unrepresentative test sample) can bias the ROC area and the validity of a comparison among tests.

Measures of Disease Probability and Bayes' Theorem Unfortunately, there are no perfect tests; after every test is completed the true disease state of the patient remains uncertain. Quantitating this residual uncertainty can be done with Bayes' theorem. This theorem provides a simple mathematical way to calculate the posttest probability of disease from three parameters: the pretest probability of disease, the test sensitivity, and the test specificity (Table 3-2). The pretest probability is a quantitative expression of the confidence in a diagnosis before the test is performed. In the absence of more relevant information it is usually estimated from the prevalence of the disease in the underlying population. For some common conditions, such as coronary artery disease (CAD), nomograms and statistical models have been created to generate better estimates of pretest probability from elements of the history and physical examination. The posttest probability, then, is a revised statement of the confidence in the diagnosis, taking into account both what was known before and after the test.

To understand how Bayes' theorem creates this revised confidence statement, it is useful to examine a nomogram version of Bayes' theorem that uses the same three parameters to predict the posttest probability of disease (Fig. 3-1). In this nomogram, the accuracy of the diagnostic test in question is summarized by the likelihood ratio for a